

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ING10692PCT	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/10118	International filing date (day/month/year) 11/09/2003	(Earliest) Priority Date (day/month/year) 13/09/2002
Applicant  INGENIUM PHARMACEUTICALS AG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 13 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (see Box II).

**4. With regard to the title,**

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ANIMAL WITH MODIFICATION OF CYTOPLASMIC DYNEIN HEAVY CHAIN 1 GENE

**5. With regard to the abstract,**

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/10118

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 27,36,42,43 (all complete);  
28-35,37-41,44,46,47,50-52,55-64,66,68-73,75-94,96-113,115-121  
(all  
partially)

Relating to modified cytoplasmic dynein heavy chain1  
polypeptides wherein the modification is an amino acid  
substitution in the wild type cytoplasmic dynein heavy  
chain1 sequence at a position corresponding to position  
Y1055 of the murine wild type sequence defined by SEQ ID  
NO:2 and polynucleotides encoding said modified polypeptides  
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Invention 2: claims 48,65 (all complete);  
39-47,50-52,55-60,63,64,66-75, 78-81,96,99-107,114-121(all  
partially)

Relating to wild type cytoplasmic dynein heavy chain1  
polypeptides and polynucleotides encoding said polypeptides  
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Invention 3: claim 49 (complete); 44,45,50,63, 64,67-77,81,97-100  
(all partially)

Relating to fragments of wild type cytoplasmic heavy chain1  
polypeptides comprising exon 13 or exons 12+13 of said  
polypeptides defined by SEQ ID NOs:21-24, and  
polynucleotides encoding said exons, defined by SEQ ID  
NOs:19 and 20.  
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Invention 4: claims 132-151, 160,162-175,177-185 (all partially)

Relating to methods of identifying mutations in an allele of  
a gene coding for a cytoplasmic dynein intermediate chain,  
using polynucleotides defined by SEQ ID NOs:30-33, 61,62,  
64-65, 70-107.  
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Invention 5: claims 132-149, 160,162-171,177-185 (all partially)

Relating to methods of identifying mutations in an allele of  
a gene coding for a cytoplasmic dynein light intermediate  
chain, using polynucleotides defined by SEQ ID NOs:34-37.  
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Invention 6: claims 132-149, 160,162-171,177-185 (all partially)

Relating to methods of identifying mutations in an allele of  
a gene coding for a cytoplasmic dynein 10 kD light chain,  
using polynucleotides defined by SEQ ID NOs:38 or 39  
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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Invention 7: claims 132-149, 160,162-171,177-185 (all partially)

Relating to methods of identifying mutations in an allele of a gene coding for a cytoplasmic dynein Tctex light chain, using polynucleotides defined by SEQ ID NOs:40 or 41

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Invention 8: claims 132-149, 160,162-171,177-185 (all partially)

Relating to methods of identifying mutations in an allele of a gene coding for a cytoplasmic dynein 2B light chain, using polynucleotides defined by SEQ ID NO:42

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Invention 9: claims 132-151, 160,162-175,177-185 (all partially)

Relating to methods of identifying mutations in an allele of a gene coding for a DCTN1, using polynucleotides defined by SEQ ID NOs:43, 44, 67, 68, 108-112, 114-158.

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Inventions 10-18: claims 132-149,160,162-171,177-185 (all partially)

As invention 9, whereby invention 10 is restricted to subject-matter related to DCTN2 defined by SEQ ID NOs:159 or 45; invention 11 is restricted to subject-matter related to DCTN3 defined by SEQ ID NOs:46 or 47; invention 12 is restricted to subject-matter related to DCTN4 defined by SEQ ID NOs:48 or 49; invention 13 is restricted to subject-matter related to DCTN5 defined by SEQ ID NO:50; invention 14 is restricted to subject-matter related to DCTN6 defined by SEQ ID NOs:51 or 52; invention 15 is restricted to subject-matter related to ARP1 defined by SEQ ID NOs:53 or 54; invention 16 is restricted to subject-matter related to ARP11 defined by SEQ ID NOs:55 or 56; invention 17 is restricted to subject-matter related to HAP1 defined by SEQ ID NOs:57 or 58; invention 18 is restricted to subject-matter related to CLIP-170 defined by SEQ ID NOs:59 or 60

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 79-81 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 82-94 and 96-100 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.2

Claims Nos.: 1-26, 28-37, 44, 53, 54, 61-66, 68, 69, 71-73, 75, 82-95, 122-131, 152-159, 161, 176 (complete); 46, 47, 50-52, 56-59, 78-81, 99, 100-121, 132-151, 160, 162-174(partially)

The present set of claims refers to an extremely large number of possible cytoplasmic dynein heavy chain1 polypeptides 'modified by substitution, deletion or insertion of at least one amino acid compared to the wild type polypeptide' and having an 'altered biological activity compared to the wild type polypeptide' and genes encoding said polypeptides. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the claimed cytoplasmic dynein heavy chain1 polypeptides and genes encoding said polypeptides.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to polypeptides and nucleic acids defined by SEQ ID NOs: 1-6 and 17-24.

In addition, the present application relates to proteins binding to the dynein/dynactin complex, defined by SEQ ID NOs representing large DNA fragments, between 78 kb and 41 Mb, which do not define the proteins for which protection is sought, since many open reading frames may be identified on said large DNA fragments. The search has been restricted to keywords and synonyms for said proteins as well as SEQ ID NOs that seem to unambiguously define said proteins, namely SEQ ID NOs:61, 62, 64, 65, 67, 68, 159.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## INTERNATIONAL SEARCH REPORT

 Intern. Application No  
 PCT/ 03/10118

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 C12N15/00 A01K67/027 C07K14/47 C07K16/18 C12Q1/68  
 C12N5/10 A61K48/00 C12Q1/68 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A01K C07K C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, Sequence Search, WPI Data, PAJ, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FAN JUAN ET AL: "Antibodies to cytoplasmic dynein heavy chain map the surface and inhibit motility" JOURNAL OF MOLECULAR BIOLOGY, vol. 307, no. 5, 13 April 2001 (2001-04-13), pages 1317-1327, XP004466061 ISSN: 0022-2836 page 1318, right-hand column, paragraph 2 figures 3,4 page 1325, right-hand column, paragraph 2 ----- -/--	42-44, 63,64

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

10 November 2004

Date of mailing of the international search report

Name and mailing address of the ISA

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Brouns, G

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TYNAN SHARON H ET AL: "Distinct but overlapping sites within the cytoplasmic dynein heavy chain for dimerization and for intermediate chain and light intermediate chain binding" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 42, 20 October 2000 (2000-10-20), pages 32769-32774, XP002292029 ISSN: 0021-9258 page 32772, left-hand column, last paragraph - right-hand column, paragraph 1 page 32769, last paragraph figures 8,9	42-44, 63,64
X	BYERS H RANDOLPH ET AL: "Role of cytoplasmic dynein in melanosome transport in human melanocytes" JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 114, no. 5, May 2000 (2000-05), pages 990-997, XP002292324 ISSN: 0022-202X page 991, right-hand column, paragraph 2 page 992, left-hand column, paragraph 3 figures 1,7,8	55-59, 61,62
X	& DATABASE UNIPROT EBI; 3 August 2000 (2000-08-03), BYERS ET AL.: "Homo sapiens cytoplasmic dynenin heavy chain mRNA, partial cds" XP002292511 Database accession no. AF234785 abstract	55-59, 61,62
X	NAGASE T ET AL: "PREDICTION OF THE CODING SEQUENCES OF UNIDENTIFIED HUMAN GENES VII. THE COMPLETE SEQUENCES OF 100 NEW CDNA CLONES FROM BRAIN WHICH CAN CODE FOR LARGE PROTEINS IN VITRO" DNA RESEARCH, UNIVERSAL ACADEMY PRESS, JP, vol. 4, no. 2, 1997, pages 141-150, XP001052821 ISSN: 1340-2838 table 2	39,45, 48,51, 52,55, 60,67, 74,78
X	& DATABASE EMBL EBI; 6 October 2001 (2001-10-06), NAGASE T ET AL.: "Human mRNA for KIAA0325 gene, partial cds" XP002292342 Database accession no. AB02323 abstract	39,45, 48,51, 52,55, 60,67, 74,78
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL EBI; 28 July 2000 (2000-07-28), SASAKI S ET AL: "Mus musculus cytoplasmic dynein heavy chain mRNA, complete cds." XP002292030 Database accession no. AY004877 abstract	60
X	----- DE ANGELIS MARTIN HRABE ET AL: "Genome-wide, large-scale production of mutant mice by ENU mutagenesis" NATURE GENETICS, vol. 25, no. 4, August 2000 (2000-08), pages 444-447, XP002292027 ISSN: 1061-4036 table 1	108-113, 116-121
P,X	----- HAFEZPARAST MAJID ET AL: "Mutations in dynein link motor neuron degeneration to defects in retrograde transport." SCIENCE (WASHINGTON D C), vol. 300, no. 5620, 2 May 2003 (2003-05-02), pages 808-812, XP002292025 ISSN: 0036-8075 the whole document	27,36, 38-44, 46,47, 50-52, 55-60, 63-81, 89-113, 115-121
Y	----- LAMONTE BERNADETTE H ET AL: "Disruption of dynein/dynactin inhibits axonal transport in motor neurons causing late-onset progressive degeneration" NEURON, vol. 34, no. 5, 30 May 2002 (2002-05-30), pages 715-727, XP002292326 ISSN: 0896-6273 cited in the application	132-151, 160, 162-185
A	the whole document	27-44, 46,47, 50-52, 55-64, 66, 68-73, 75-94, 96-113, 115-121
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## INTERNATIONAL SEARCH REPORT

Intern Application No  
PCT/03/10118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ROGERS DEREK C ET AL: "SHIRPA, a protocol for behavioral assessment: Validation for longitudinal study of neurological dysfunction in mice" NEUROSCIENCE LETTERS, vol. 306, no. 1-2, 22 June 2001 (2001-06-22), pages 89-92, XP002292026 ISSN: 0304-3940 the whole document	108-121
A	MARTIN MARYANN ET AL: "Cytoplasmic dynein, the dynactin complex, and kinesin are interdependent and essential for fast axonal transport" MOLECULAR BIOLOGY OF THE CELL, vol. 10, no. 11, November 1999 (1999-11), pages 3717-3728, XP002292325 ISSN: 1059-1524 cited in the application table 1 figures 1,2	108-121
X	VAUGHAN P S ET AL: "Cytoplasmic Dynein Intermediate Chain Phosphorylation Regulates Binding to Dynactin" JOURNAL OF BIOLOGICAL CHEMISTRY 13 JUL 2001 UNITED STATES, vol. 276, no. 28, 13 July 2001 (2001-07-13), pages 26171-26179, XP002304788 ISSN: 0021-9258	177-182
Y	figures 2,5,8	132-150, 160, 162-174, 183-185
X	SUSALKA STEPHEN J ET AL: "The roadblock light chain binds a novel region of the cytoplasmic dynein intermediate chain" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 36, 6 September 2002 (2002-09-06), pages 32939-32946, XP002304789 ISSN: 0021-9258 figure 6	177-182
Y	page 32943, left-hand column	132-150, 160, 162-174, 183-185
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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/03/10118

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KOPEC KARLA ET AL: "Effect of Alzheimer's brain extracts on dynein immunoreactivity in PC12 cells"</p> <p>PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE, vol. 216, no. 3, December 1997 (1997-12), pages 429-437, XP008038429</p> <p>ISSN: 0037-9727</p> <p>the whole document</p> <p>-----</p>	<p>132-149, 160, 162-171, 173, 177-185</p>

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: Application No

PCT/03/10118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0153312	A	26-07-2001	
		US 6569662 B1	27-05-2003
		AU 2292401 A	31-07-2001
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